

AWARD NUMBER: W81XWH-15-2-0026

TITLE: Clinical Evaluation of Decellularized Nerve Allograft With Autologous Bone Marrow Stem Cells To Improve Peripheral Nerve Repair and Functional Outcomes

PRINCIPAL INVESTIGATOR: LTC Leon Nesti MD PhD

RECIPIENT: Henry M. Jackson Foundation for the Advancement of Military Medicine Inc.
Bethesda, MD 20817

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TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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4. TITLE AND SUBTITLE Clinical Evaluation of Decellularized Nerve Allograft With Autologous Bone Marrow Stem Cells To Improve Peripheral Nerve Repair and Functional Outcomes				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-2-0026	
				5c. PROGRAM ELEMENT NUMBER	
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. Bethesda, MD 20817				8. PERFORMING ORGANIZATION REPORT NUMBER	
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12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution is unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The current award is a phase I safety study (n=12) evaluation of the synergistic effect of the co-treatments of a commercially available decellularized processed peripheral nerve allograft scaffold (Avance® Nerve Graft, AxoGen, Alachua FL) with autologous bone marrow stem cells (BMSC) for the reconstruction of mixed peripheral nerve gaps between 3 and 7 cm in length. Each treatment separately has been shown to have an established safety record. Avance has been used in more than 10,000 surgeries without a reported adverse event. The current standard of care for nerve injury, the autograft, has significant limitations: the source and quantities of autologous tissue needed for repairs are limited, and when faced with severe trauma these donor sites are not viable due to concurrent injury. Use of a decellularized nerve graft mitigates concerns of donor site morbidity, decreases surgical time and has substantially equivalent outcomes. Augmenting the scaffold with the patient's own BMSCs may allow for point of care treatment with the potential to enhance the regenerative ability of the wound-healing environment. The proposed use of an existing commercially available scaffold with an autologous stem cell transplant, both with proven safety records, would establish a safety profile and provide a proof of principle for this type of approach.					
15. SUBJECT TERMS Avance nerve graft, autologous bone marrow stem cells (BMSC), nerve autograft, peripheral nerve repair					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION:

The purpose of this study is to evaluate the safety of the nerve allograft and BMSC sequentially to repair peripheral nerve gaps of the ulnar and median nerves of the upper extremities between 2 and 7 centimeters (cm) in length. Subjects will be followed for 18 months post-surgery. Secondary outcomes will be examined to evaluate the efficacy of the co-treatment for nerve repair compared to Avance Nerve Graft and BMSC treatments alone. The study is designed to treat up to 24 patients using the sequential treatment of nerve allograft and BMSC. This is a prospective, observational trial to evaluate the safety of Avance nerve graft and BMSC and to measure the efficacy of the synergistic treatment for peripheral nerve repair.

2. KEYWORDS:

Avance nerve graft
Autologous Bone Marrow Stem Cells (BMSC)
Nerve autograft
Peripheral nerve repair

3. OVERALL PROJECT SUMMARY:

The goal for the award was to accomplish Major Task 1 Startup in months 1-6. Sub tasks 1.1 – 1.6 have been completed. Sub task 1.5 and 1.7 Prepare case report form and IRB Protocol is still pending. Major Task 2 IRB/HRPO approval has not been undertaken. The first three months of the award did not result in progress as the Program Manager was not hired until month 4 and the Clinical Coordinator was not hired until month 6 (Subtasks 1.1 and 1.2). In months 7 - 9 subtask 1.3 and 1.4 database and site preparation were completed. Site Training including CITI training occurred in month 8. Subtask 1.5 and 1.7 complete case report and finalize scientific review and IRB submission are still pending as of the end of month 12.

Reasons for the sustained delays are due to three major reasons. The first reason is due to changes in the WRNMMC IRB submission system and changes to the IRB submission templates which required additional effort (1 mo) to redo the completed work to date to the new format. An additional delay (1 mo) has been due to the introduction of a new eIRB submission system and the training required to learn and use the new system. The second reason for the delays are due to the difficulties encountered by the PI having awards run by the Geneva Foundation and this award run by HJF. Personnel issues and the negotiation of personnel agreements (still not executed) further delayed progress (2 mo). The final reason for the delays are the difficulty of the regulatory and strategy decisions that were unanticipated in the original SOW. Working with our clinical trial sites and commercialization partner AxoGen along with Cleveland Clinic took longer than anticipated. Re-evaluation of the enrollment numbers and the sequence of the proposed interventions has led to changes in the proposed SOW that will be submitted to the GOR for review in year 2. Completion of Major Task 1 and the start of Major task 2 is anticipated in Q2 of year 2. It is still anticipated that all interventions will be completed before the end

of year 3 with follow-up of the research subjects will require a No Cost Extension (NCE) as disclosed in the submitted quarterly reports.

4. KEY RESEARCH ACCOMPLISHMENTS

No Key Research accomplishments beyond what was outlined in the overall project summary above have been accomplished.

5. CONCLUSION:

Year one progress was not considered satisfactory. Many startup activities and staffing did occur and progress towards submission of the case report forms and protocol occurred, but as of month 12 have not been finalized and submitted.

The following reasons for this lack of progress have been identified. Staffing occurred starting three months late. The PI having different awards run by multiple foundations (Geneva and HJF) and sharing staffing through personnel agreements has proven to be impossible to execute and sustain. Changes to the eIRB submission system and adoption of new templates also caused delays. Finally the difficulty of the proposed regulatory strategy and the enrollment assumptions have taken longer to finalize and determine.

Future plans are to finalize the case report forms and protocol (Q1 Yr 2) and to submit to the SRC (Q2 Yr 2) and full IRB submission (Q3 Yr 2). It is anticipated that the PI will move all staffing to HJF given the unsatisfactory working relationship with the Geneva Foundation. One unanticipated future delay is the possible military deployment of the PI starting in Q3 Year 2 for 100 days.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

Publications: Nothing to report

Abstracts: Nothing to report

Presentations: Military Nerve IPR on 2/4/16 Fort Detrick (attached)

7. INVENTIONS, PATENTS AND LICENSES:

Nothing to report

8. REPORTABLE OUTCOMES

Nothing to report

9. OTHER ACHIEVEMENTS:

Nothing to report

10. REFERENCES:

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11. APPENDICES:

None

12. TRAINING OR FELLOWSHIP AWARDS:

None

13. COLLABORATIVE AWARDS:

No collaborative awards were executed in year 1

14. QUAD CHART:

See attached



Clinical Evaluation of Decellularized Nerve Allograft with Autologous Bone Marrow Stem Cells



to Improve Peripheral Nerve Repair and Functional Outcomes

Award: 81XWH-15-2-0026 Log No: MR140132

PI: LTC Leon Nesti M.D. Ph.D.

Org: USUHS

Requested Amount: \$2.3M (d+id)

Study/Product Aim(s)

The proposed project is to conduct a phase I safety and proof-of-premise clinical evaluation of the synergistic effect of co-treatments of a commercially available decellularized processed peripheral nerve allograft scaffold combined with autologous bone marrow stem cells (BMSC) for the reconstruction of mixed peripheral nerve gaps between 3 and 7 cm in length.

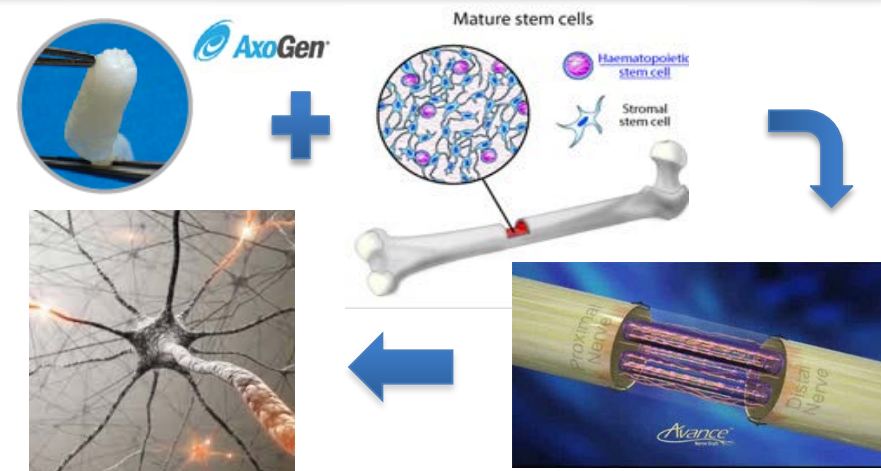
Approach

Number of Total Research Subjects: n=12

Clinical Trial Sites: 4 (WRNMCC, SAMMC, CNHC)

Anticipated Enrollment: 1 patient to enroll every 3 mo

Regulatory Status: BLA being prepared for FDA submission for Avance Nerve Graft. RECON Study cleared for enrollment.



Accomplishment: All IRB documents drafted

Timeline and Cost

Avance BMSC Phase I Trial	Year 1				Year 2				Year 3				NCE				
Summary Gantt Chart	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4					
Major Task 1 Start-up																	
Major Task 2 SRC/IRB/HRPO Approval																	
Major Task 3 Enrollment																	
Major Task 4 Intervention																	
Major Task 5 BMSC Culture & Analysis																	
Major Task 6 Follow Up																	
Major Task 7 Analysis																	
Major Task 8 Close Out																	

Delays will likely push Intervention requiring NCE for follow up and analysis

EST. (\$K)	Yr 1 \$610K	Yr 2 \$850K	Yr 3 \$840
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Goals/Milestones

Yr 1 Goals

- ☒ Start Up, Hire PM, Identify Staff, Project Planning, Organization, Doc Prep
- ☐ SRC/IRB /HRPO (SRC 10/16 IRB 11/16, HRPO 12/16)
- ☐ Enrollment & Interventions Begin
- ☐ BMSC Culture & Analysis Begins

Yr 2 Goals

- ☐ Enrollment & Interventions Complete
- ☐ Follow Up Begins

Yr 3 Goals

- ☐ BMSC Culture & Analysis Complete

NCE Goals

- ☐ Follow Up Complete
- ☐ Study Analysis
- ☐ Closeout & Publication

Comments/Challenges/Issues/Concerns: Staffing/Strategy/eIRB

Budget Expenditure to Date

Projected Expenditure: \$610K

Actual Expenditure: \$286K

V11 Updated 7/15/16



**In-Progress
Review
(IPR)
Meeting**

Nerve

**4 February
2016**

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Clinical Evaluation of Decellularized Nerve Allograft with Autologous Bone Marrow Stem Cells to Improve Peripheral Nerve Repair and Functional Outcomes

PI: LTC Leon Nesti MD PhD

01 July 2015 – 30 June 2018 (POP)

\$2.3M (d+i)

Program Director: Christian Walker MS MA MBA



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Nerve

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Military Relevant Issue To Be Solved

- **Capability Gaps:** Repair of large segmental nerve defects
- **Research Question:** Are decellularized scaffolds & autologous stem cells safe when used together in a human clinical trial?
- **Benefits of Knowledge Gained:** Provide clinical validation for approach and justification for additional development & funding

Project Funding



Current Budget

\$ \$2.3M

Expended Funds

\$ 95K

%

4%

Projected Prime expenditure to date: \$165K WRNMMC

Projected sub-contract to date: \$200K (\$0 spent)

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Statement of Work

Conduct a phase I safety and proof-of-premise clinical evaluation of the synergistic effect of co-treatments of a commercially available decellularized processed peripheral nerve allograft scaffold combined with autologous bone marrow stem cells (BMSC) for the reconstruction of mixed peripheral nerve gaps.



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Hypothesis / Primary Outcome

- **Hypothesis:** The combination of decellularized allograft and autologous BMSC will have the same or better safety profile and demonstrate an improvement in the quality of nerve regeneration when compared to the current standard of care, autograft, and Avance[®] alone in a phase I clinical safety evaluation.
- **Primary Outcome:** Assess the safety profile of the processed nerve allograft when combined with autologous BMSC's as a treatment for reconstruction of mixed peripheral nerve gaps.

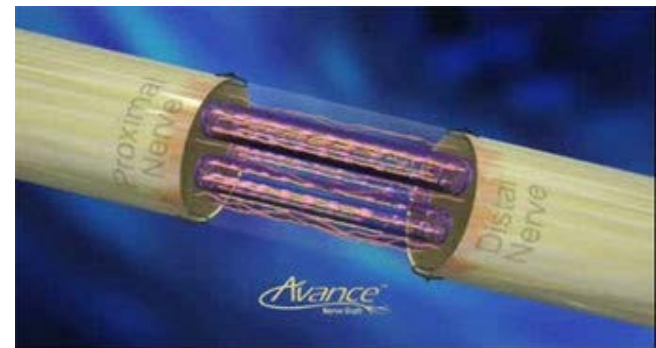
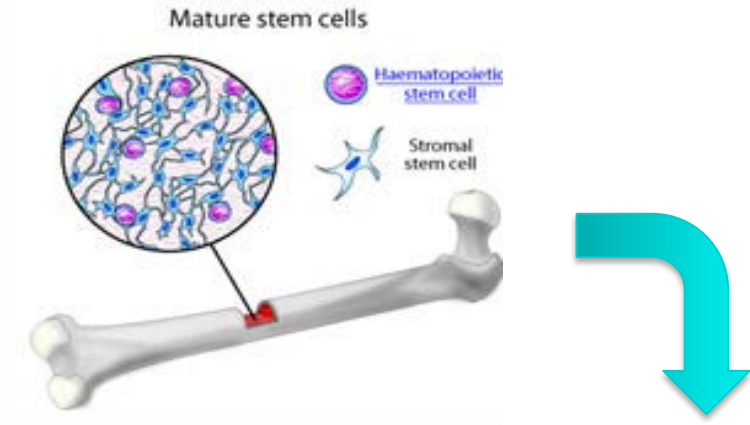


Summary Overview

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Approach

Stage: Phase I Safety & Proof of Principle

Number of Total Research Subjects: n=12

Clinical Trial Sites: 4

WRNMCC

SAMMC

CNHC

MUSC

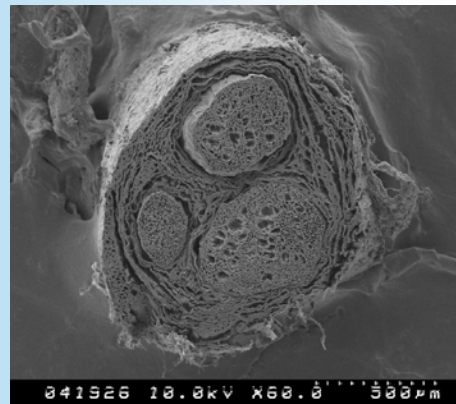


Analysis: Cleveland Clinic

Anticipated Enrollment: 1 patient every 3 mo



Commercial Partners



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Research/Development Timeline



Original Gantt

Avance BMSC Phase I Trial		Year 1				Year 2				Year 3			
Summary Gantt Chart		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Major Task 1	Start-up												
Major Task 2	IRB /HRPO Approval												
Major Task 3	Enrollment												
Major Task 4	Intervention												
Major Task 5	BMSC Culture & Analysis												
Major Task 6	Follow Up												
Major Task 7	Analysis												
Major Task 8	Close Out												

Current Gantt

Avance BMSC Phase I Trial		Year 1				Year 2				Year 3				NCE	
Summary Gantt Chart		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4		
Major Task 1	Start-up														
Major Task 2	SRC/IRB/HRPO Approval														
Major Task 3	Enrollment														
Major Task 4	Intervention														
Major Task 5	BMSC Culture & Analysis														
Major Task 6	Follow Up														
Major Task 7	Analysis														
Major Task 8	Close Out														

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Challenges

Strategy: Site of Injury and Application of BMSC

Programmatic: WRNMMC IRBnet down

Contracting: Currently billed as onsite at USUHS but conducted offsite at WRNMMC

Recruitment: Conflicts winding down

Regulatory: FDA Guidance on Homologous Use (Pending)



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Intellectual Property / Publications

Patents Issued:

- ❖ Harvest Technologies
- ❖ AxoGen (3 Issued License from UT and UF)

Confidentiality Agreements: None

Invention Disclosures: None

Publications: None



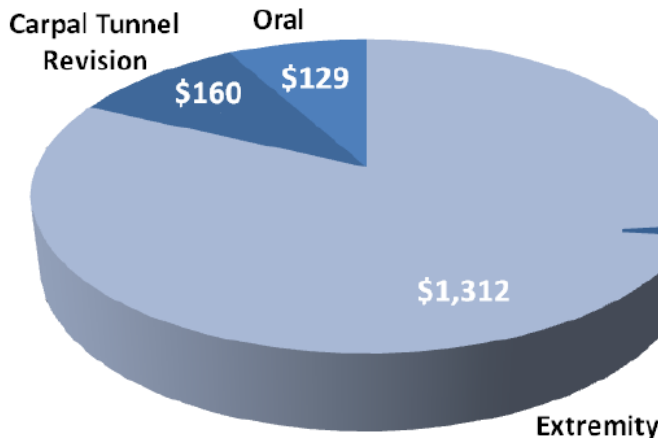
Total vs Addressable Market Size

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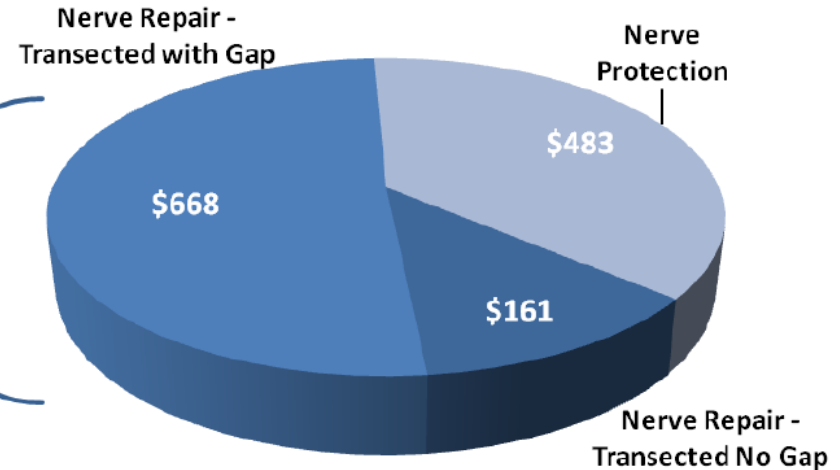
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AxoGen Current Target Market
\$1.6 billion
In millions



Extremity Market
\$1.3 billion
In millions



Approximately 900K Procedures in US:

Extremity	719,000
Carpal Tunnel	100,000
Oral	68,000

Assume equal distribution between short, medium large gap, if so large gap market size is maximum \$220M



Cost / Reimbursement

- Autograft is billed as a procedure
- Allograft not insurance reimbursed
- Allograft saves need for second surgery
- Average cost of Operating Room per Hour \$9K
- Allows hospitals to rebook OR 2X
- Hospitals pay break even cap of \$4.5K

Autograph Procedure



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Transition/ Business/ Marketing Plan

- Avance a 361 tissue transitioning to a BLA
- BMSC an FDA cleared POC medical device
- No future product development envisioned
- Safe scaffold when used in conjunction with safe stem cell is safe
- Provides clinical validation & justification for continued investment in scaffold stem cell

Additional Project Information



**In-Progress
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Nerve

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Lab/Company/Group: WRNMMC Dept of Orthopedics

Principal Investigator: LTC Leon Nesti MD PhD

Grants Officer Representative: Mary Alice Woody PhD

Government Project Officer: Blossom Widder

Contract Instrument: Cooperative Agreement

Period of Performance: 01 July 2015 – 30 June 2018

Contract Specialist: Chris Meinberg

Contract #: 81XWH-15-2-0026 Log # MR140132